MAEDICA - a Journal of Clinical Medicine

CASE REPORTS

MAEDICA – a Journal of Clinical Medicine
2014; 9(1): 62-67

Metastatic Melanoma in the Femur – Case Report with Review of Literature: a Pathologist's Point of View

Mariana COSTACHE[a]; Alexandra STOICA[b]; Andreea CONTOLENCO[b]; Diana COSTACHE[c]; Catalin CIRSTOIU[d]; Olga SIMIONESCU[e]; Simion GEORGE[b]

[a]Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[b]Department of Pathology, Emergency University Hospital Bucharest, Romania
[c]„Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[d]Department of Orthopaedics and Traumatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[e]Department of Dermatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

The aim of this case report was to evaluate the histopathological characteristics on a patient with metastases in the femur from malignant melanoma. A review from the literature is also mentioned.

We present a case of metastatic malignant melanoma in the femur with known primary site in a 44-year-old-female. Diagnosis was confirmed by histopathology.

Malignant melanoma is a cancer that may metastasise in the skeleton. However most of bone metastases are found in the axial skeleton and they rarely involve the femur, as in our case. Only a few case reports are published in the literature. Clinicians must be aware of the varied clinical manifestations of disseminated malignant melanoma.

The diagnosis for metastatic malignant melanoma is confirmed due to pathological examination. Immunohistochemical study is useful in diagnosis, mainly when malignant melanoma is poorly differentiated.

Keywords: metastases, malignant melanoma, femur

Address for correspondence:
Mariana Costache, Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, 8 Eroilor Sanitari Avenue, 050474, Bucharest, Romania.
E-mail: m_costache_dermatopat@yahoo.com.

Article received on the 18th of July 2013. Article accepted on the 5th of March 2014.

INTRODUCTION

Malignant melanoma is a neoplasm and it describes a malignant proliferation of melanocytes in the skin mainly, but also in other organs like the esophagus, the oral and anogenital mucosa, the eyes and the meninges (1,2). Even though it represents only 3 to 5% of primary cutaneous malignancies, malignant melanoma remains the most aggressive one (3). The incidence of this type of cancer has increased a lot over the last decades. Nowadays, malignant melanoma is responsible for 50% of deaths from skin cancer (3).

In order to reduce mortality due to melanoma is very important to recognise and to excise completely the primary lesions, because once the cancer metastasise, the therapy is complicated and ineffective most of the times and also the prognostic is poorer (4).

Histological diagnosis of melanoma is based both on cytological and architectural criteria, but often the cytological criteria are less important than the architectural ones.

Microscopically, melanoma cells are pleomorphic (rounded, fusiform with different sizes); they have large and irregular shaped nuclei with chromatin being typically clumped at the periphery of the nuclear membrane; the nucleoli have often a reddish colour also known as "cherry red".

The growth pattern of malignant cells is described as arranging into nests or as single cells in epidermis then extending into dermal, and form balloon-like nodules.

This pattern describes the radial and then vertical growth phase of the malignant melanoma.

It has been proven that the depth of invasion in millimeters (Breslow thickness) determines the biological behavior of melanoma.

Malignant melanoma less than 0,76 mm thick usually does not give metastasis to any organs and does not require excision of the proximal lymph nodes, whereas melanoma greater than 1,5 mm thick usually presents greater risk of lymph node metastases than the previous one (5).

Metastatic melanoma or clinical stage 4 melanoma is described when the malignant melanocytes spread from the primary site to the regional or distant lymph nodes and to other organs (6).

According to OMS, Stage IV Melanoma is divided into 3 subclasses (M1a, M1b, M1c).

First the metastases pass beyond the regional lymph nodes and spread to distant skin, the subcutaneous layer, distant lymph nodes. Then M1B stage describes lung invasion. M1C describes two situations: in the first case, the infiltration of a distant organ, other then the lung, and in the second case, the elevation of LDH with any site metastasis (7,8).

Usually, distant metastases are detected after a few years from the excision of the primary tumor (although late metastases, from 10 to 25 years are not uncommon in this type of cancer).

The regional lymph nodes are invaded first, before other organs, but there are also cases of hematogenous spread of malignant cells. In those cases the patients had distant visceral metastases without involvement of the lymph nodes (9).

The metastatic behavior of malignant melanoma is uncommon because the sites of metastases are widespread compared to other tumors. Even if, in theory, any organ can be invaded by malignant cells, melanoma commonly spreads in certain organs more than in others. It will metastasise mainly in the following organs: skin (other areas), subcutaneous tissue and lymph nodes (50-75%), lungs and area between the lungs (70-87%), liver (54-77%), brain (36-54%), bone (23-49%), gastrointestinal tract (26-58%), heart (40-45%) adrenal glands (36-54%), kidneys (35-48%), spleen (30%), and others (9-11).

When distant metastases appear, the most important factor associated with the survival of the patient is the number of invaded organs and also the type of the metastases (visceral disease has a poorer outcome) (12-14). ❑

CASE REPORT

A 44-year-old female presented in February 2009 at University Emergency Hospital Bucharest (Emergency Department), complaining of severe pain and functional impotence in the right hip. Some pains in the right thigh and gluteal region were present for about four months, but at a lower intensity.

At physical examination, during active and passive mobilisation attempts, major pain in the hip and functional impotence were highlighted. Palpation revealed a regional deforma-

tion in the right thigh with globular aspect, that measured about 25/12 cm, without precise limits, adherent to adjacent tissues and with no signs of local inflammation. The radiography of the right femur in front incidence, revealed a shaft incomplete fracture on pathological bone. The patient had been admitted with a diagnosis of proximal third right femur fracture on pathological bone, for specialised investigations and treatment.

The admission diagnosis was fracture on pathological bone because the patient was known with grade 4 malignant melanoma. On 2003 an excisional biopsy of a pigmented tumour was made and the histopathological diagnosis was malignant melanoma without any details about prognostic parameters (Clark level and Breslow thickness). Back then, the patient followed courses of chemotherapy. After that, on 2005 liver metastases were diagnosed.

The whole-body scintigraphy examination realised on the third day of hospitalisation revealed a retention area with high intensity and heterogeneous character in the proximal third of the right femur (trochanteric and shaft region). The scapulo-humeral and the hip joint had a medium retention (with an inflammatory character). On SPECT/CT examination, small areas of medium retention and heterogeneous character were present; it is also described the fracture trajectory marked on CT.

The conclusions were: there was probably a tumor with high radioisotope retention on the fracture area.

The laboratory analysis revealed an inflammatory syndrome with leukocytosis (white blood cells were 13,3*103/mm^3 (normal values 4-9*103/mm^3)), neutrophilia (neutrophils were 83,6% (N: 43-65 %)) and lymphocytopenia (9,2% (N: 20,5-45,5 %)), the fibrinogen was 497 (N: 200-400 mg/dL) and erythrocyte's sedimentation rate was 28 (N: 5-10 mm/h). Also a hepatic cytolysis syndrome was present (AST: 82 U/L (N: 2-40 U/L)) and some coagulation disorders: PT: 15 (11-13 sec), INR: 1,21 (0,92-1,14).

The surgery was performed and consisted of large resection of the tumor. A reconstruction arthroplasty with total hip replacement has been done. The prosthesis used was Revital type, with cemented cup.

After 2 days the patient began to gradually mobilize and she was discharged 15 days after surgery.

Five months later, the patient presented again at E.R. complaining of pain and functional impotence in the left shoulder. The local examination revealed a regional deformation and during active and passive mobilization attempts, pain and functional impotence were highlighted.

The patient was admitted with the diagnosis of bone metastasis of melanoma in the left shoulder area, with assumption of humeral metastasis. In her medical history, besides the already known femural and liver metastases, were mentioned lung and brain metastases. Therefore, even if the evolution after hip arthroplasty was favourable, general condition of the patient was worse because new metastases appeared. No laboratory analysis or other tests results were found on this last medical record probably because the patient was transferred to the Department of Oncology. ❑

DISCUSSION

Malignant melanoma is a cancer that may metastasise in the skeleton (15,16). Usually, the bone is the site for metastases of the prostate, kidney, breast and thyroid cancers.

Metastatic malignant melanoma is more likely to disseminate to skin, lungs, liver and brain (17). In most studies, bone metastases of malignant melanoma are present in a proportion ranging from 11% to 17%. However, the autopsy results revealed the existence of a higher percentage of bone involvement: 23-49%. Studies have shown that 80% of bone metastases from malignant melanoma are found in the axial skeleton (skull, ribs, vertebral column and pelvis) (18). Metastases in the proximal third of the femur, as in our case, are rare. In the literature are published only a few case reports.

Bone lesions from malignant melanoma usually occur in patients who already have widespread metastases, thereby it is a late site of metastasis. In this case the average survival is assessed from 2 to 6 months.

Because clinical diagnosis of bone metastases is rare, little information has been publish about the natural history, the laboratory and imaging features.

Typically the patient presents to the doctor for localized pain that gradually increases, and for functional impotence. As in our case, occurrence of acute pain could signify a pathological fracture. Also, systemic manifestations

such as fever, fatigue, weight loss, nausea, constipation, thirst, confusion can occur, but less frequently; and they are the consequence of increased serum calcium levels.

Diagnosis of metastatic malignant melanoma is based on specific skin lesions associated with investigations like: blood tests, bone X-ray, CT, MRI, PET scanning, biopsy, pathological examination, immunohistochemistry. Blood tests are used to determine serum calcium levels (hypercalcemia) and serum LDH levels. Serum LDH levels are used as a marker of progressive metastatic disease and as a negative prognostic factor. Frequently, blood LDH levels are normal even in late-stage of metastatic melanoma. Other blood tests have not proven to be useful in order to indicate the presence and/or prognosis of metastases.

Bone metastases may be visible on X-ray but as long as the cortical remains intact, most medullary lesions are radiographically occult. The most common findings visible on the X-ray are osteolytic lesions with poorly defined limits, as in our case. Other aspects less common are sclerotic or mixed lesions or a periosteal reaction. The lesions can sometimes affect the bone marrow (19). Radiographic lesions are not characteristic (20). CT is more accurate than the X-ray and it detects axial skeletal metastases in about 15% of patients with melanoma, compared to scintigraphy (10%) (21). MRI aspects are not well described; however in a case study of spinal metastases from malignant melanoma the authors noted an increased T1 signal in bone (22). On PET scanning, pathological bone absorbs the radioactive substance, so metastases appear as "hot spots".

The diagnosis is confirmed due to pathological examination which can describe isolated tumoral cells or tumoral islands with pleomorphic appearance (characterised by several sizes or aspects), trachychromatic and voluminous nuclei with atypical mitosis and brown pigment in cytoplasm; we can see neoplastic embolus of melanoma cells (Figure 1). It can also be associated with necrosis. The tumour infiltrates and destroys the bone (Figure 2). Immunohistochemical study is useful in diagnosis when malignant melanoma is poorly differentiated. Melanoma is typically reactive for vimentin, HMB-45, S-100 protein, tyrosinase, melan-A and microphthalmia transcription factor. HMB-45 is a marker more specific than S-100 protein.

Treatment of bone metastases of malignant melanoma can be curative or palliative, and it includes: surgery, chemotherapy, radiotherapy, biological therapy, combination therapy (chemotherapy combined with biological agents) (23). It has been proven that combination therapy, as an initial treatment, gives a higher response rate and long-term remissions (24).

The aim of treatment is to reduce the symptoms, fracture risk and the risk of hypercalcemia. Treatment of bone metastatic malignant melanoma consists in prevention and treatment of pathological fracture. On the other hand, treatment may be used to reduce symptoms, this way improving the quality of life. Chemotherapy and radiation are prescribed based on protocols that continue to evolve, as

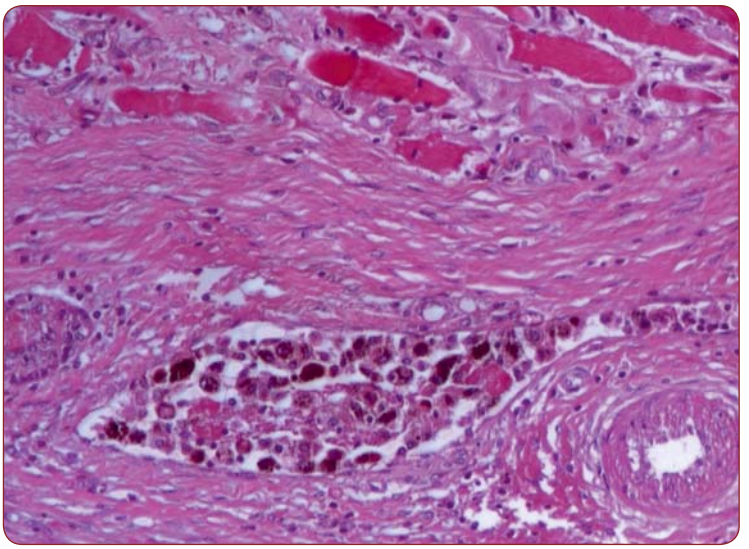

FIGURE 1. Neoplastic embolus of melanoma cells; striated muscles fibres; HE 100x.

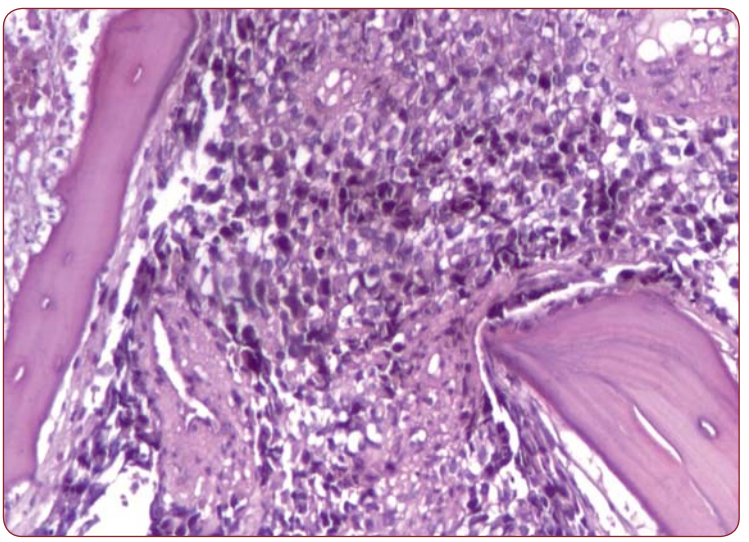

FIGURE 2. Melanoma cells infiltrated the bone; HE 100x.

new drugs appear. These can slow the progression of metastatic melanoma, but not to cure it.

Clinical trials for metastatic melanoma estimated that the 5 year survival rate for stage 4 melanoma is 3% and the average survival rate is 4 months (24). The prognostic is better when only bone metastases are present and worse when visceral metastases are associated. One author demonstrated that there are no differences regarding life expectancy between melanoma metastases from the appendicular skeleton and those situated on the axial skeleton (25).

The patients who underwent surgery for prevention of pathological fractures have a much better evolution than those in whom surgery was performed for a fracture already present. These patients have shorter hospitalization duration, faster recovery and have longer survival with fewer surgical complications. ❑

CONCLUSION

Malignant melanoma is a cancer that may metastasise in the skeleton. Research of the bibliography showed that most of bone metastases from malignant melanoma are found in the axial skeleton and they rarely involve the femur, as in our case. Up to this moment, few cases such as this have been reported. Based on this background, we felt it is important that clinicians and pathologists must be aware of the varied clinical manifestations of disseminated malignant melanoma.

The diagnosis for metastatic malignant melanoma is confirmed due to pathological examination. Immunohistochemical study is useful in the diagnosis, mainly when malignant melanoma is poorly differentiated.

Conflict of interests: none declared.
Financial support: none declared.

References

1. **McCartney RA –** Melanoma. In: Gale T, Longe J. Gale Encyclopedia of Cancer, second Edition. Detroit: Ed. Gale Group, 2005; 672-677
2. **Lazar A –** The Skin. In: Kumar V, Abbas A, Fausto N, Mitchell R. Robbins and Cotran Basic Pathology, 8th Edition. Philadelphia: Ed. Saunders Elsevier Inc. 2007; 856-859
3. **Jani M, Borrelli J –** Orthopedic Injuries. In: Humphrey P, Dehner L, Pfeifer J. The Washington Manual of Surgical Pathology. Philadelphia: Lippincott Williams & Wilkins, 2008; 1116-1126
4. **Rosenberg A –** Bones, Joints and Soft Tissue Tumors. In: Kumar V, Abbas A, Fausto N, Mitchell R. Robbins and Cotran Pathologic Basis of the Disease, 8th Edition. Philadelphia: Ed. Saunders Elsevier Inc. 2010; 856-859
5. **Elder DE, Elenitsas R, Murphy GF, et al. –** Benign Pigmented Lesions and malignant Melanoma. In: Elder DE. Lever's Histopathology of the skin, tenth edition. Philadelphia: Lippincott Williams & Wilkins, 2009; 738-775
6. **McKee P, Calonje E, Granter S –** Melanoma. In: McKee P, Calonje E, Granter S. Pathology of the skin with clinical correlations, third edition, Philadelphia: Elsevier Mosby, 2005; 1309-1355
7. **Suster S, Wong TY, Mihm MC –** Tumors of the Skin. In: Weidner N, Cote RJ, Susner S, Weiss LM. Modern Surgical Pathology, second Edition. Philadelphia: Ed Sauders Elsevier Inc., 2009; 1936-1942
8. **Mills S –** Melanocityc Lesions. In: Mills S, Carter D, Greensom J, Reuter V, Stoler M. Sternberg's Diagnostic Surgical Pathology, 5th Edition. Philadelphia: Lippincott Williams & Wilkins, 2010; 91-99
9. **Elder DE, Thompson JF –** Malignant Melanoma. In: Kleihues P, Sobin L. World Health Organization Classification of Tumors – Pathology & Genetics. Skin Tumors. Lyon: Ed. IARCPress, 2006; 52-79
10. **Meyers ML, Balch CM –** Diagnosis and treatment of metastatic melanoma. In: Balch CM, Houghton AN, Sober AJ, Soong S-J (eds). Cutaneous Melanoma.3rd Edition. St. Louis: Quality Medical Publishing, 1998; 325-372
11. **Akslen LA, Hove LM, Hartveit F –** Metastatic distribution in malignant melanoma. A 30-year autopsy study. Invasion & Metastasis 1987; 7(5): 253-263
12. **Sim FH, Nelson TE, Pritchard DJ –** Malignant melanoma: Mayo Clinic Experience. *Mayo Clinic Proceedings* 1997; 72:565-569
13. **Yeu-Tsu N –** Malignant melanoma: Pattern of metastasis. *A Cancer Journal for Clinicians* 1980; 30:137-142
14. **Barth A, Wanek LA –** Prognostic Factors in 1,521 Melanoma Patients with Distant Metastases. *Journal of the American College of Surgeons* 1995; 181 (3):193-201
15. **Fon G, Wang W, Gold R, et al. –** Skeletal metastases of melanoma: radiographic, scintigraphic and clinical review. AJR American Journal of Roentgenology 1981; 137(1):103-108
16. **Pattern R, Shuman W, Teefey S –** Metastases from malignant melanoma to the axial skeleton: a CT study of frequency and appearance. *American Journal of Roentgenology* 1990; 155(10):109-112
17. **Stevens G, Firth I, Coates A –** Cerebral metastases from malignant melanoma. *Radiotherapy and Oncology* 1992; 23:185-191
18. **Brountzos E, Kelikis D, Panagioutou I, et al. –** Bone metastases from malignant melanoma: a retrospective review and analysis of 28 cases. *Radiology and Oncology* 2001; 35(3):209-214
19. **Deepali J, Kuman N, Daga M –** Metastatic malignant melanoma in bone marrow with occult primary site – a case report with review of literature. *Diagnostic Pathology* 2007; 2:38-39
20. **Konefal JB, Emami B, Pilepich MV –** Analysis of dose fractionation in the palliation of metastases from malignant melanoma. *Cancer* 1988; 61:243-246
21. **Katz HR –** The results of different fractionation schemes in the palliative irradiation of metastatic melanoma. *International Journal of Radiation Oncology* 1981; 7:907-911

22. **McMenamin D, Stuckey S, Potgieter G –** T1 hyperintense vertebral column melanoma metastases. *American Journal of Neuroradiology* 2007; 28(9):1817-1818
23. **Einhorn L, Burgess A, Vallejos C, et al. –** Prognostic Correlations and Response to Treatment in Advanced Metastatic Malignant Melanoma. *Cancer Research* 1989; 34:1995-2004
24. **Rigel DS, Carucci JA –** Malignant melanoma: Prevention, early detection, and treatment in the 21st century. *A Cancer Journal for Clinicians* 2000; 50:215-236
25. **Patel JK, Didolkar MS, Pickren JW, et al. –** Metastatic pattern of malignant melanoma: A study of 216 autopsy cases. *The American Journal of Surgery* 2011; 135:807-810.